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Hydroxychloroquine Prophylaxis for COVID-19

David D. Busath
Brigham Young University, david_busath@byu.edu

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David D. Busath, M.D.

Professor of Physiology and Biophysics (retired), Brigham Young University, Provo, UT 84602

david_busath@byu.edu, 801 369-6366

Abstract: It is common in medicine that simple, inexpensive remedies are held hostage to medical prejudice, financial or political interest, and legal precedent. The purpose of this review is to take the point of view of the victims of COVID-19 and address whether scientific information, including randomized-control trials, can answer whether the hydroxychloroquine should be dispensed for those testing positive and their immediate recent contacts at the point of testing. Although the FDA in the United States is yet to be convinced, the demonstration of positive effects in clinical trials cannot be ignored and there is a large amount of information in the pipeline (published pre-prints and registered clinical trials) that could tip the scales towards making the drug readily available for early disease and contact-prophylactic usage to reduce peak symptoms, symptom duration, contagiousness, hospitalizations and mortality.

In the past few years, the original promise of the influenza neuraminidase inhibitor oseltamivir (Tamiflu), has been realized in many states in the USA that now allow it to be dispensed in pharmacies, often in conjunction with rapid diagnostic testing (1). This has been facilitated by the termination of patent rights and development of generics, but inhibited by bias in the medical community, which is familiar with clinical trials confirming their experience that oseltamivir only shaves a day or two off of symptoms when administered "within 36 hours" of the onset of symptoms (2) and the ethical and clinical complexities (3). Physicians may be less familiar with the carefully controlled human influenza exposure experiments demonstrating that if given the day before or day after infection, it dramatically reduces the magnitude and duration of symptoms (4). Influenza has a short incubation period (1-2 days) and even when administered at the onset of symptoms, oseltamivir is very effective. Later treatment is not effective because the symptoms are mainly an expression of the immune system inflammation, which is usually sufficiently effective to confine and eliminate the virus in the lungs.

When the COVID19 pandemic began, hydroxychloroquine (HCQ) and chloroquine were rational choices for prophylaxis. With a modest *in vitro* potency and low cytotoxicity for SARS-COV2 (5-8), about one tenth as strong as oseltamivir's potency against influenza, basic scientists projected that it might be weak, but available and useful in reducing symptoms if given early in the infections. Its possible role in a respiratory virus pandemic situation had been discussed for over a decade.

Early clinical trials of HCQ for COVID19 were undertaken where it was most convenient, i.e. with hospitalized patients. Focusing here on peer-reviewed publications, most reports were for retrospective observational or cohort studies and some showed good reduction of infection rate, hospital course, and/or death (9-17) while others showed little or no effect (18-23). An editorial in *Science* (24) citing the negative conclusion of the Recovery trial at Oxford proclaimed that only large RCTs should be trusted. But in this scenario, reproducibility in observational studies clearly justified further study.

A preprint report of one of the latter studies posted on April 23, (now published (20)), which is a retrospective cohort analysis of COVID19 patients in all US Veteran Affairs hospitals admitted up until April 11, yielded higher mortality for the HCQ arm than the standard of care arm and caused a large academic and public reaction. Coinciding with increasing concerns about long QT arrhythmia risk at high doses in a phase IIb HCQ trial in Brazil published on April 24 (25), some clinical trials were discontinued or put on hold. Several studies of QT prolongation in hospitalized patients subsequently showed only modest QTc prolongation for patients on HCQ with no cases of *torsades de pointes* (26-30). A safety review concluded that "HCQ should not be restricted in COVID-19 patients out of fear of cardiac morality" (31). After a period of time, some clinical trials resumed but many of these have reported poor enrollment due to the negative publicity that week. One carefully executed randomized control trial showed no reduction in viral RNA load for non-hospitalized patients, but results may have been diluted by using patients with up to five days of symptoms at enrollment (32).

Early hopes that a prophylactic effect of HCQ were suggested by a use in an outbreak situation in a Korean hospital (33), a small study in Hubei province, China (34), and a low case frequency in countries where malaria is endemic (35). One might hope to find a prophylactic effect in patients taking it continuously for systemic lupus erythematosus or rheumatoid arthritis, but by mid-June these hopes were doused by reports of COVID19 appearing in these populations taking HCQ with frequencies similar to those not (36), consistent with a massive study published July 8 of the similar incidences of COVID19 in rheumatoid (a large fraction presumably taking HCQ) vs. non-rheumatoid groups (37). However, these apparent neutral results do not account for an increased incidence of COVID-19 in rheumatoid patients, which when considered yielded a protective effect of HCQ (38). Furthermore, a retrospective study of rheumatoid patients in Portugal demonstrated a significant reduction in COVID-19 vulnerability in HCQ users (39).

Prophylaxis (40) and early treatment (41) RCTs carried out by internet recruitment and overnight-shipped tablets (HCQ or folic acid placebo) showed no or modest effects, respectively. The World Health Organization discontinued the Solidarity later treatment trial for “little or no reduction in mortality.” Subsequently, numerous additional observational studies and RCTs, including a few pre- and post-exposure prophylaxis and early treatment have been published. Most have demonstrated positive effects (42-56) and a few have shown little or no effect (57-62). Some of the clinical trials have been analyzed for bias potential with stringent criteria (63-65), but an ever-present possibility of editorial bias. The recent studies show persuasive, reproducible benefits of HCQ in humans against COVID-19.

Animal studies showed that HCQ is ineffective against SARS-COV2 infections instilled in ferrets (66), and cynomolgus macaques (67). The ferrets were treated one day post-infection and showed some reduction of inflammation signs, but viral load was unaffected. The monkeys were treated either one hour after or seven days before infection and showed no reduction in viral load in the early treatment case, nor reduction in infection rate in the pre-exposure prophylaxis case. In conjunction with the macaque study, it was also shown that a human airway epithelium model derived from biopsies was not protected from SARS-COV2 infection by HCQ (67).

On June 15, the FDA in the USA revoked its emergency use authorization for HCQ out of concerns over cardiotoxicity, as suggested in an informative but pessimistic April 20 review (68). They currently recommend that HCQ only be used for COVID19 under the auspices of a registered clinical trial. Medical institutions and pharmacies reigned in the physicians who believed HCQ was useful and were prescribing it as routine practice. This drew a law suit from the American Association of Physicians and Surgeons against the FDA (pending in federal court in Grand Rapids, Michigan, AAPS v. FDA, et al., 20-cv-493) and stimulated the formation of the American Frontline Physicians who were persuaded of the HCQ clinical merits from their personal experience. Stephen Hatfill, a bioterrorism expert, and Harvey Frisch, an epidemiologist, weighed in on August 4 in a RealClear Politics article and August 23 in a

television interview, respectively, that there are many clinical trials that show a benefit for HCQ in COVID19, and that it has not yet been tested for prophylactic effect in vulnerable populations. Most studies so far have focused on critically ill late-stage inpatients, or slightly ill young healthy outpatients. Perhaps prophylaxis for vulnerable subjects is where HCQ will prove effective (69). On one hand, a strong argument about the inadequacy of standard dosing and cardiotoxicity at adequate dosing was published on August 17 (70). On the other hand, national use of HCQ correlates with reduced nation case fatality rates (71).

At this point (September 29, 2020), we can say with confidence that HCQ does not immediately reverse COVID19 for hospitalized patients, but it also doesn't cause increased mortality (reference (20) notwithstanding), and for some it may be helpful. We can say that taking HCQ chronically for rheumatological disease may or may not protect one appreciably, but the negative results may be confounded by high vulnerability of such patients to COVID-19, or perhaps chronic use may lead to cellular adaptation. In young healthy infected respondents to on-line surveys, it is moderately better than placebo for reducing symptoms and the chance of hospitalization, although statistical significance wasn't achieved (41).

But yet needed are the kinds of studies that could motivate the health care industry and the FDA to make HCQ available at the point of rapid SARS-COV2 testing. It is easy to imagine that such studies might yet appear. For instance, given the low risk of severe disease in healthy young adults, it is easy to imagine a research experiment like the original oseltamivir experiment where 100 individuals are recruited to isolate in hotel rooms and get exposed to SARS-COV2 with HCQ or placebo. No such experiment is currently being contemplated to my knowledge.

More immediately, we eagerly await the publication of many registered pre-print reports of clinical trials. An excellent summary of this literature, as well as plots of global use of HCQ and COVID-19

incidence divided by nations that allow HCQ use and those that limit it, can be found at c19study.com. The count of positive-effect pre-print reports greatly exceeds that of non-effect reports, but these are yet to be peer-reviewed, evaluated for bias-potential, and weighed for significance as they relate to cost, risk, and benefit.

We also await the results of more registered clinical trials for HCQ used as early and prophylactic treatment against COVID19. As of August 25, there were 247 clinical trials registered at clinical trials.gov identified with the keywords "COVID19, hydroxychloroquine." Of particular interest are the 67 selected with the keywords "COVID19, hydroxychloroquine, prophylaxis." Of these, 25 have titles indicating that they are focused on the use of HCQ prophylaxis in health care workers for COVID19, namely NCT04435808, NCT04364815, NCT04303507, NCT04438837, NCT04437693, NCT04352946, NCT04363450, NCT04377646, NCT04333225, NCT04354597, NCT04336748, NCT04370015, NCT04345653, NCT04384458, NCT04374942, NCT04340349, NCT04334928, NCT04354870, NCT04318015, NCT04371926, NCT04347889, NCT04328285, NCT04346329, NCT04334148, NCT04371523. In addition, there were 60 trials in the WHO COVID19 Registry retrieved with the keywords "chloro, prophyl" or "chlor outpatient" (where keywords can be parts of words). Although many studies have been canceled out of fear of cardiotoxicity in the investigators or potential subjects, it is possible that some will yet be completed in the next 6 months or so, as many originally projected.

There are also a few prophylaxis studies underway in vulnerable populations, such as nursing homes. These include the PREVICHARM trial (NCT04400019), a Canadian study (NCT04397328), a multicenter study based in Chicago, New Orleans, Boston and other sites (NCT04354428), and the French OUTCOV study (NCT04365582). The first two of these were retrieved from clinicaltrials.gov with the keywords stated above, and the second two with the keyword "prophylaxis" replaced with "outpatient." These vulnerable population studies are the most difficult to arrange, not just because of ethical concerns that such subjects would be more sensitive to long QT syndrome, or at least to the

dehydration that could accompany any vomiting associated with nausea and diarrhea, common initial side effects of HCQ, but also because nursing homes could be hard to place under the watch of internal review boards from hospitals, universities, or other large institutions. But, these may be the most important studies yet to be done, because the world is most frozen by the fear of COVID19 wiping out these vulnerable populations *en masse*. The level of concern for the vulnerable is demonstrated by the arguments that children, teens, and college students should wear masks at school and healthy adults should wear masks to the grocery store and workplace when neither group is likely to have deadly illness if they contract COVID19.

However, the larger set of prophylaxis studies with health care workers is probably most important for the question of whether states should allow pharmacies to dispense HCQ under a standing doctor's order for clients with positive rapid SARS-COV2 saliva tests. Only if HCQ safely flattens the curve for healthy individuals on a personal-symptoms level sufficient to impress the FDA would HCQ be appropriately dispensed at pharmacies. In many countries, HCQ is available over the counter for malaria prophylaxis. One can hope that the FDA will soon be convinced to make HCQ, readily available to the common victims of COVID-19. Then whether it is done under a doctor's standing order prescription at pharmacies and sites that perform rapid testing or just over-the-counter would be up to state legislatures.

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